

## Motor “Dexterity”? Evidence that Left Hemisphere Lateralization of Motor Circuit Connectivity Is Associated with Better Motor Performance in Children

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**Motor control relies on well-established motor circuits, which are critical for typical child development. Although many imaging studies have examined task activation during motor performance, none have examined the relationship between functional intrinsic connectivity and motor ability. The current study investigated the relationship between resting state functional connectivity within the motor network and motor performance assessment outside of the scanner in 40 typically developing right-handed children. Better motor performance correlated with greater left-lateralized (mean left hemisphere—mean right hemisphere) motor circuit connectivity. Speed, rhythmicity, and control of movements were associated with connectivity within different individual region pairs: faster speed was associated with more left-lateralized putamen–thalamus connectivity, less overflow with more left-lateralized supplementary motor–primary motor connectivity, and less dysrhythmia with more left-lateralized supplementary motor–anterior cerebellar connectivity. These findings suggest that for right-handed children, superior motor development depends on the establishment of left-hemisphere dominance in intrinsic motor network connectivity.**

**Keywords:** development, motor control, resting state network

### Introduction

A network of regions subserving motor control develops relatively early compared with other brain networks (Lin et al. 2008; Dubois et al. 2009), although motor development may continue through adolescence (Larson et al. 2007; Cole et al. 2008). The development of motor systems is fundamental for a range of academic (e.g., handwriting), social, and communicative skills (Gidley Larson and Mostofsky 2006; Viholainen et al. 2006; Fuentes et al. 2009; Iverson 2010) and abnormal or delayed motor development is characteristic of a number of neurological disorders including autism and attention deficit hyperactivity disorder (ADHD) (Garvey et al. 2005; Mostofsky et al. 2006, 2007, 2009; Shaw et al. 2007; Suskauer et al. 2008). Therefore, better understanding of the typical development of motor control may be important in characterizing these disorders.

Motor control recruits a set of brain regions involved in coordinating, sequencing, refining, and selecting movements. Neuroscience, neuropathology, and imaging studies implicate a well-defined network in motor control. Discrete thalamo-cortical–basal ganglia and thalamocortical–cerebellar loops form segregated circuits subserving different functions including motor control (Alexander et al. 1986; Middleton and Strick 1997; Akkal et al. 2007; Haber and Calzavara 2009). A reliable network of regions involved in motor control have

been found in studies examining task activation during repetitive or sequential movements (Holsapple et al. 1991; Scholz et al. 2000; Solodkin et al. 2001; Mostofsky et al. 2006, 2009), as well as in studies examining resting state networks (Biswal et al. 1995; Guye et al. 2003; Damoiseaux et al. 2006; Postuma and Dagher 2006; Di Martino et al. 2008; Krienen and Buckner 2009; Robinson et al. 2009; Barnes et al. 2010; Habas 2010).

Regions consistently implicated in basic motor control include primary motor (M1), the supplementary motor complex (SMC), which encompasses the supplementary motor area (SMA) and more rostral pre-SMA, as well as thalamus, putamen, and anterior cerebellum. Although these regions form an intrinsically connected network, there is evidence that individual regions subserve distinct motor functions. Striatal (putamen) circuits are critical to refining the direction, amplitude, and speed of movements (DeLong, Alexander, et al. 1984; van Donkelaar et al. 2000). The SMC is involved in response selection and sequencing of movements (Akkal et al. 2007; Mostofsky and Simmonds 2008; Nachev et al. 2008). Medial and anterior aspects of the cerebellum play a role in refining movements and the ongoing correction of smooth pursuit movements (Konczak and Timmann 2007; Lisberger 2010). Interhemispheric connections between primary motor regions are important for selecting movements (Garvey et al. 2005). While these regions perform distinct aspects of motor control, they act in concert to execute refined, complex actions.

Unilateral movements recruit a contralateral motor circuit (including ipsilateral cerebellum and medial SMC), while more complex movements rely on bilateral activation to a greater degree (Scholz et al. 2000; Solodkin et al. 2001; Mostofsky et al. 2006, 2009). Although limb movements depend on activation in the contralateral motor circuit, research suggests that the 2 hemispheres of the motor circuit may not play equivalent roles in motor control (i.e., lateralization may exist). In right-handed individuals, there are structural differences between the hemispheres which include greater depth of the left central sulcus, greater left M1 volume (Amunts et al. 1996), and larger left globus pallidus volume (Kooistra and Heilman 1988). A functional study found that left M1 activates to a similar degree during left-hand and right-hand finger movements, however, right M1 only shows activation during contralateral left-hand finger movements (Kim et al. 1993). In addition, whole-brain functional connectivity with left M1 is more extensive than with right M1 (Guye et al. 2003).

Although functional differences exist between the left and right motor circuits, it is unclear how these differences contribute to motor abilities. Greater connectivity in the

contralateral hemisphere could predict better motor abilities for limb movements. Alternatively, greater connectivity in the left as compared with the right hemisphere (i.e., left-hemisphere dominance) could predict motor abilities. In the current study, intrinsic functional connectivity was examined in right-handed children to determine whether left- or right-hemisphere connectivity predicts motor abilities. Pairwise connectivity within each circuit was compared with children's motor abilities as assessed outside of the scanner by the Physical and Neurological Examination for Subtle Signs (PANESS) motor battery (Denckla 1985). Motor seed regions were placed at peak coordinates previously found using functional magnetic resonance imaging (fMRI) while subjects performed a simple motor task (Mostofsky et al. 2009). Connectivity was examined as the mean of the  $z$ -transformed correlations for all region pairs within each hemisphere of the motor network and also the difference between the two hemispheres (left-right-lateralized connectivity) to determine the contribution that overall network connectivity makes to motor ability. Connectivity between each of the region pairs within left-hemisphere (LH) and right-hemisphere (RH) circuits were examined to determine whether intrinsic connectivity between specific regions contribute to specific motor abilities. In addition, the interhemispheric primary motor connection was examined to determine its role in motor abilities.

## Materials and Methods

### Participants

40 healthy, typically developing right-handed children (21 female, 19 male) participated in the study. Children were between 8 years 0 months and 12 years 11 months of age (mean = 10.20, standard deviation [SD] = 1.06). All participants had normal Full Scale IQ on the Wechsler Intelligence Scale for Children (mean = 112.07, SD = 10.45) with no history of intellectual disability, developmental language disorder, reading disability, pervasive developmental disorder, visual impairment, neurologic disorder, nor psychiatric diagnosis, as confirmed using the DICA-IV (Sala et al. 2006). Only subjects with movement of less than 3 mm translation and 3 degree rotation over the course of the resting scan were included in the current sample.

This study was approved by the Johns Hopkins Medical Institutional Review Board. Written consent was obtained from a parent or legal guardian and assent was obtained from the participating child.

### Behavioral Motor Assessment

Participants were assessed for motor performance outside of the scanner using the PANESS. The PANESS is a standardized battery of motor control which is sensitive to developmental changes in children's motor abilities, including balance, coordination, and speed (Denckla 1985). It examines these functions and codes for the presence of motor signs, including overflow and dysrhythmia, during performance of gait, station, and timed limb movements. The PANESS has been normed in large samples of children (Denckla 1973, 1974; Gidley Larson and Mostofsky 2006) and has been validated for test-retest reliability (Holden et al. 1982), inter-rater reliability, and internal consistency (Vitiello et al. 1989). The Gaits and Stations portion of the examination includes gait and balance movements, such as walking on the heels, toes, sides of feet, and tandem. The Timed Movements portion of the examination includes performance of repetitive, simple flexion/extension movements (finger tap, hand pat, toe tap, and side-to-side tongue movements), and more complex patterned movements (i.e., heel-toe tap, hand pronate-supinate, finger sequence). Participants are timed to completion of 10 or 20 movements. Timed movements are measured in seconds and then are gender and age normalized by converting to  $Z$ -scores (Denckla 1985).

Overflow and dysrhythmia are measures of inefficient or immature motor function. Overflow refers to the occurrence of unintended and unnecessary movements that mimic the voluntarily executed movement. Overflow movements are assessed during both gait and timed maneuvers. This may include proximal/orofacial overflow, in which movement occurs in proximal musculature unnecessary to intended motor execution (e.g., wrist flexion/extension or jaw opening/closing during finger tapping) and mirror overflow, in which contralateral movements mimic the intended motor execution. Dysrhythmia refers to inappropriate timing or sequencing of movements.

Dependent measures of motor function derived from the PANESS include: 1) Total PANESS score, which is a composite measure of performance across the entire examination (reflecting both trunk and limb movements), 2) Total Timed score, a composite measure of speed, overflow, and dysrhythmia during all timed movements, 3) Total Gaits and Stations score, a composite measure of speed, overflow, and dysrhythmia during gaits and stations, and 4) separate composite measures of Overflow, Speed, and Dysrhythmia across all Timed movements.

### fMRI Acquisition and Processing

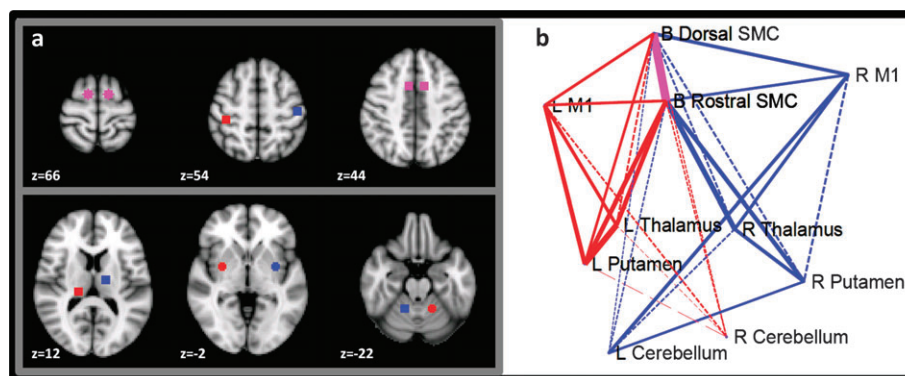
Motor circuit connectivity was examined across each participant's resting state run. In order to minimize movement, children performed a mock scan the day before testing in which they were instructed to stay as still as possible. During testing, resting state scans were acquired for 5 min 20 s using a 3-T Philips scanner (2D-SENSE EPI, 8-channel head coil, time repetition = 2500 ms, time echo = 30 ms, Flip angle = 70°). Participants were instructed to relax, stay as still as possible, and fixate on a center cross. Preprocessing of functional images included slice time correction, motion correction, normalization, removal of nuisance variables: cerebrospinal fluid, white matter, and global mean using CompCor (Behzadi et al. 2007) and 6 motion parameters, 6 mm full-width at half-maximum spatial smoothing, and temporal filtering (0.01–0.1 Hz band-pass filter).

### Data Analysis

Six-millimeters-radius 3D seeds were placed at coordinates for the left and right motor circuits (Fig. 1*a*). These networks were previously identified during right-handed and left-handed finger sequencing (Mostofsky et al. 2009). Task activation for these regions was generally contralateral to the motor movement, with the exception of ipsilateral cerebellum and medial SMC, which extended across both hemispheres for movements on both sides. SMC seeds were placed at both a rostral and a dorsal location, since these regions may be associated with different motor functions (Suskauer et al. 2008; Mostofsky et al. 2009). Previous examination has distinguished the caudal part of the SMC, which is posterior to the anterior commissure (AC), from the rostral SMC. The caudal SMC has direct connections to primary motor cortex and has been implicated in response sequencing and coordination of complex movements, while the rostral SMC has connections with prefrontal regions and has been implicated in more "cognitive" functions such as conflict monitoring and response preparation (Mostofsky and Simmonds 2008; Nachev et al. 2008). The rostral SMC coordinates for the current paper were identified during a finger-tapping task and although they are anterior to the AC line, they lie close to coordinates previously implicated in response selection (Picard and Strick 2001; Simmonds et al. 2008).

The LH motor circuit (right-side movements) included left M1, left thalamus, left putamen, bilateral SMC-rostral, bilateral SMC-dorsal, and right anterior cerebellum seeds. The RH motor circuit (left-side movements) included right M1, right thalamus, right putamen, bilateral SMC-rostral, bilateral SMC-dorsal, and left anterior cerebellum seeds.

Time series from seed regions were extracted and pairwise correlations were performed within the LH and RH motor circuits separately using Pearson's correlation and then converted to a normal distribution using Fischer's  $z$  transform. Mean network connectivity was determined by averaging the  $z$ -transformed correlations between all region pairs within a hemisphere. Brain-behavior relationships were then assessed by simple regression of each subject's  $z$ -transformed



**Figure 1.** Motor circuit seed regions. (a) LH seed regions in red and RH seed regions in blue, bilateral SMC seeds are shown in pink. (b) Graph theoretic depiction of the motor circuit. LH connections are displayed in red and RH connections are displayed in blue. The pink edge between dorsal and rostral SMC is common to both hemispheres. Line widths correspond to connection strength. Solid lines represent significant connections after multiple comparisons corrections (for 29 connection pairs). Dashed lines represent subthreshold connections.

**Table 1**

The relationship between composite PANESS scores and motor circuit connectivity

	Difference LH–RH connectivity
Total paness	$R = -0.555, P = 0.0002$
Total timed	$R = -0.583, P = 0.0001$
Total gaits and stations	$R = -0.361, P = 0.022^*$
Overflow	$R = -0.546, P = 0.0003$
Dysrhythmia	$R = -0.445, P = 0.004$
Speed	$R = -0.275, P = 0.086$

\*The significance of the effect changed when the outlier subject was removed.

pairwise region correlation or mean hemispheric connectivity to PANESS scores.

For PANESS assessment, better performance is associated with lower scores. Faster speed results in lower speed scores and more efficient movements result in less overflow and dysrhythmia. Only the Z-normalized speed scores result in the opposite relationship. Better motor performance (i.e., faster speed) is associated with higher normalized Z-scores.

## Results

### Behavioral PANESS Scores

For the current sample, total PANESS scores ranged from 8 to 49 with a mean score of 22. One subject performed at 2.5 SDs above the mean for all PANESS scores. Results were computed both with and without this outlier subject. For most brain–behavior correlations (except Total Gaits and Stations, see Table 1), exclusion of this subject did not change the significance or the direction of the effect. For this reason, the results are reported with the outlier included. Cases in which the outlier changed or drove the effect are noted.

The relationship between hand preference and motor function was examined to determine whether the relationship between motor abilities and motor network laterality may be due to handedness. Hand preference was assessed using the Edinburgh Handedness Inventory (Oldfield 1971). The relationship between Total PANESS and Edinburgh Handedness score was not significant ( $R = 0.15, P = 0.36$ ).

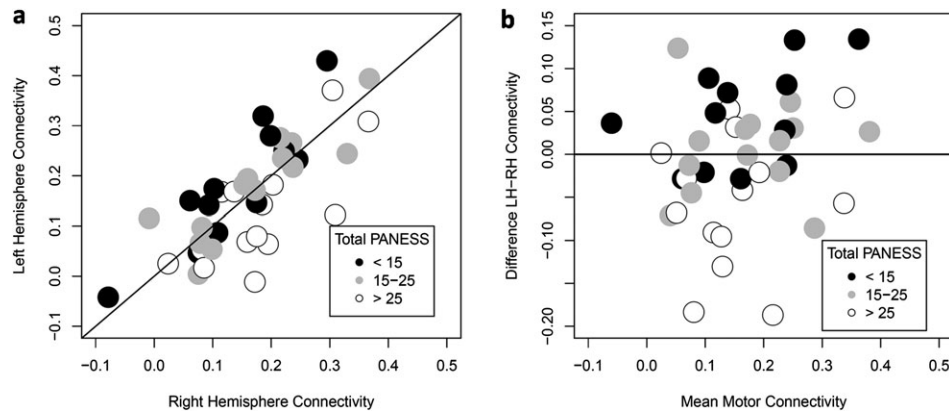
### Network Connectivity and Composite PANESS Measures

Pairwise connectivity between each of the region pairs within the LH and RH were computed (Fig. 1b). Z-transformed correlations for each of the 15 pairs within a hemisphere were then averaged to get the mean LH and mean RH connectivity for each subject. Examination of the mean hemispheric connectivity revealed that mean motor connectivity for right and left hemispheres is highly correlated across participants ( $R = 0.757, P = 0.0001$ ).

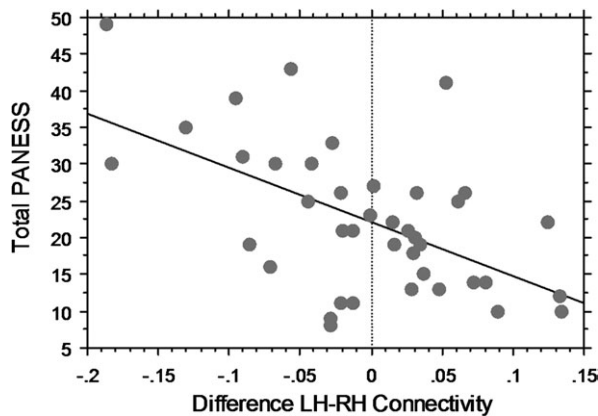
Figure 2a displays the mean hemispheric connectivity and the relationship with Total PANESS scores. Lower PANESS scores indicated by black dots tend to be associated with stronger left than right-hemisphere connectivity. Because of the high correlation in mean connectivity between the 2 hemispheres, we transformed the data into the mean connectivity  $(LH + RH)/2$  and the lateralized difference in hemispheric connectivity  $(LH - RH)$ . Figure 2b demonstrates that lateralization appears to be related to Total PANESS (i.e., the majority of black dots lie above the horizontal line, while the majority of open dots lie below). In contrast, average connectivity appears unrelated. These results are borne out by regression models, where the lateralized difference was significantly correlated with lower (better) total PANESS (Fig. 3:  $R = -0.55, P = 0.0002$ ), while mean connectivity was not ( $R = 0.001, P = 0.995$ ), in both simple correlations (reported here) and joint regression models including both terms (see Supplementary Material). Similarly, models including only left-hemispheric connectivity, not adjusting for right, and analogously right-hemispheric connectivity, not adjusting for left, showed no association with total PANESS (LH:  $R = -0.18, P = 0.259$ ; RH:  $R = 0.21, P = 0.18$ ), as these models are roughly equivalent to considering average connectivity. Thus, in what follows, we focus on results for correlation of lateralized hemispheric differences (LH–RH) in connectivity with measures of motor function.

As with Total PANESS scores, nearly every PANESS composite score showed an association between better motor performance and greater left-lateralized motor circuit connectivity (Table 1), including Total Timed (Fig. 4:  $R = -0.58, P = 0.0001$ ), Overflow (Fig. 5:  $R = -0.55, P = 0.0003$ ), and Dysrhythmia ( $R = -0.44, P = 0.004$ ). Although the Total Gaits and Stations score was also correlated with left-lateralized connectivity ( $R = -0.36$ ,

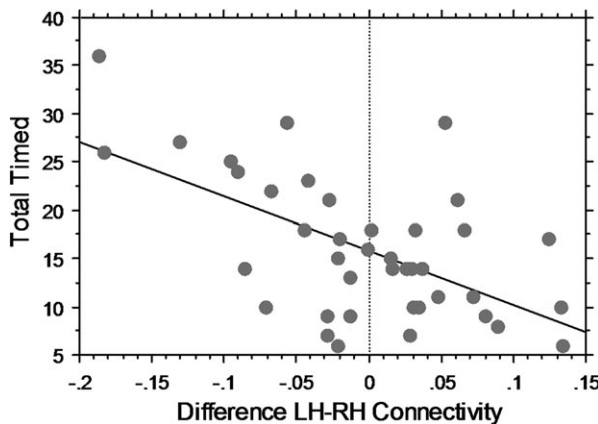




**Figure 2.** Relationship between total PANESS and mean hemispheric connectivity. (a) LH and RH connectivity. (b) Difference LH-RH connectivity and mean connectivity.



**Figure 3.** Relationship between lateralized (LH-RH) motor connectivity and Total PANESS scores.



**Figure 4.** Relationship between lateralized (LH-RH) motor connectivity and Total Timed scores.

$P = 0.02$ ), this correlation was weaker than that of other PANESS scores and the relationship did not remain significant with the removal of the outlier subject. The only measure that was not significantly associated with LH-RH network connectivity was the speed of timed movements ( $R = -0.27$ ,  $P = 0.09$ ).

To determine whether primary motor interhemispheric connections influence motor abilities, the strength of the

connection between left and right M1 was examined. Within the current study, primary motor interhemispheric connection strength was not significantly associated with motor abilities ( $R = -0.07$ ,  $P = 0.67$ ). In addition, the degree of right-handedness was compared with motor network connectivity to determine whether connectivity may reflect the degree of hand preference. Edinburgh Handedness score was not significantly related to mean connectivity within either hemisphere or to the LH-RH difference (LH:  $R = -0.13$ ,  $P = 0.42$ ; RH:  $R = -0.23$ ,  $P = 0.16$ , LH-RH:  $R = 0.09$ ,  $P = 0.54$ ). To determine whether handedness affects the relationship between lateralized connectivity and PANESS, partial correlation, controlling for handedness, was performed. The  $r$  value for this relationship was  $-0.579$  and the  $P$  value was  $0.0001$ . The correlation between lateralized connectivity and PANESS, without controlling for handedness, was  $-0.555$  and the  $P$  value was  $0.0002$  suggesting that handedness had little effect on this brain-behavior relationship.

To ensure that the relationship between lateralized connectivity and motor abilities is specific to the motor network, 3 multiple regression models were computed, which compared Total PANESS with mean and lateralized connectivity within 3 brain networks: motor, default mode, and visual. Default mode network seeds were taken from peak seed regions identified using resting state connectivity (Fox et al., 2005). Visual seeds were regions selected within BA 17 and BA 19. (see Supplementary Material). Total PANESS scores were significantly predicted by lateralized connectivity in the motor network ( $R = -0.568$ ,  $P = 0.0007$ ) but not the other 2 network models (DMN:  $R = 0.26$ ,  $P = 0.26$ ; visual network:  $R = 0.33$ ,  $P = 0.11$ ). The beta coefficient for lateralized visual network connectivity was significant and this relationship was in the opposite direction as lateralized motor network connectivity (Supplementary Table S2). However, only the motor network model was significant. These analyses suggest that the relationship between left-lateralized connectivity and Total PANESS scores is specific to the motor network.

### Age and Gender

Analysis of Variance tests were performed with age bins (8, 9, 10, and 11-12 years) and gender (M, F) as random factors. For the current sample, there were no significant age or gender effects for either mean motor circuit connectivity (gender:

$F_{1,4,30} = 5.26, P = 0.079$ ; age:  $F_{3,3} = 1.37, P = 0.40$ ; age x gender:  $F_{3,32} = 0.30, P = 0.83$ ) or LH-RH circuit connectivity (gender:  $F_{1,3,30} = 1.99, P = 0.245$ ; age:  $F_{3,3} = 0.118, P = 0.944$ ; age x gender:  $F_{3,32} = 1.32, P = 0.29$ ). There were also no significant effects for total PANESS (gender:  $F_{1,3,30} = 0.48, P = 0.534$ ; age:  $F_{3,3} = 0.12, P = 0.943$ ; age x gender:  $F_{3,32} = 1.25, P = 0.309$ ).

To determine whether age affects the relationship between lateralized connectivity and PANESS, partial correlation, controlling for age, was performed. The  $r$  value for this relationship was  $-0.556$  and the  $P$  value was  $0.0002$ . The correlation between lateralized connectivity and PANESS, without controlling for age, was  $-0.555$  and the  $P$  value was  $0.0002$ . Therefore, age had little effect on this brain-behavior relationship in the current cohort.

### Pairwise Brain-Behavior Correlations

Pairwise correlations were performed for each of the region pairs to determine whether particular connections were important for specific aspects of motor performance (Supplementary Table S3). For these analyses, timed movement Overflow, Speed, and Dysrhythmia subscales were compared with lateralized connectivity in each region pair. For each of the specific comparisons, the  $P$  value was multiplied by 14 to correct for multiple comparisons. Overflow was significantly

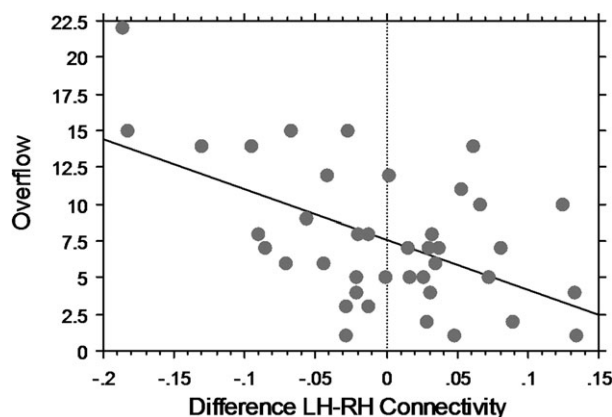
associated with LH-RH rostral SMC-M1 connectivity (Fig. 6:  $R = -0.49, P = 0.001$ ). This relationship was significant for left-side movements ( $R = -0.52, P = 0.0005$ ) and typically developing (TD) for right-side movements ( $R = -0.42, P = 0.007$ ), but the latter relationship did not hold up after multiple comparisons correction. Dysrhythmia was marginally associated with lateralized cerebellum-rostral SMC connectivity ( $R = -0.40, P = 0.01$ ) and speed was marginally associated with lateralized putamen-thalamus connectivity ( $R = -0.38, P = 0.02$ ). Although these relationships did not reach significance after multiple comparisons correction, they are notable because they are consistent for both left-side (left Dysrhythmia and lateralized cerebellum-rostral SMC:  $R = -0.37, P = 0.02$ ; left Speed and lateralized putamen-thalamus:  $R = -0.32, P = 0.04$ ) and right-side movements (right Dysrhythmia and lateralized cerebellum-rostral SMC:  $R = -0.32, P = 0.04$ ; right Speed and lateralized putamen-thalamus:  $R = -0.39, P = 0.01$ ).

### Discussion

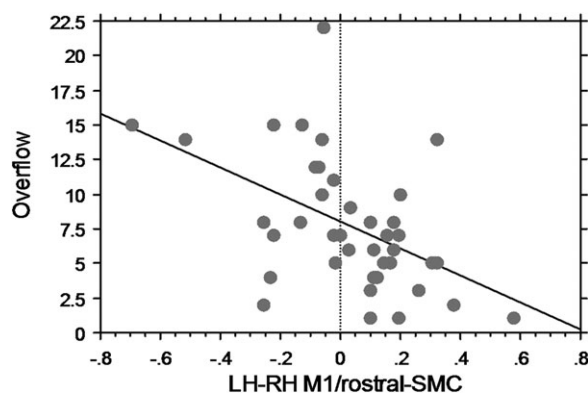
The current study examined the relationship between intrinsic functional connectivity in RH and LH motor networks and motor abilities in typically developing (TD) right-handed children. This is the first study to apply resting state functional connectivity to examine brain-behavior relationships between motor network connectivity and motor control abilities and replication in an independent sample is necessary to confirm this relationship. We found consistent and robust relationships between children's motor abilities and the degree to which connectivity was stronger within the LH motor circuit than it was within the RH circuit, that is, LH motor connectivity dominance. Greater left-lateralized motor circuit connectivity not only predicted overall better motor ability, reflected in Total PANESS score, it also predicted several other specific measures, including Total Timed, Overflow, and Dysrhythmia scores. The consistency of the findings across motor measures supports the observation that left-lateralized motor connectivity is associated with superior motor performance in children.

Analyses of specific region pairs revealed specific brain-behavior associations, with lateralized connectivity in distinct region pairs correlating with specific motor signs. The most robust of these was the correlation between left-lateralized SMC-M1 connectivity and Overflow. Although the rostral part of the SMC has been implicated in such cognitive functions as conflict monitoring and response preparation (Picard and Strick 2001; Mostofsky and Simmonds 2008; Mostofsky et al. 2009), the coordinates of this seed region were close to regions previously implicated in response selection (Menon et al. 2001; Picard and Strick 2001; Rubia et al. 2001) and therefore, may play a role in motor execution. The SMC has direct projections to M1, which influence the selection of appropriate movements and the inhibition of inappropriate movements (Picard and Strick 2001; Akkal et al. 2007; Mostofsky and Simmonds 2008; Nachev et al. 2008; Simmonds et al. 2008). The current findings are in accordance with previous studies examining SMC function and they suggest that SMC-M1 connections are important for the selection of precise motor commands.

In addition, we found left-lateralized putamen-thalamus connectivity was associated with speed and that left-lateralized cerebellum-SMC connectivity was associated with dysrhythmia; however, these findings did not survive correction for multiple comparisons. Nevertheless, the findings are interesting



**Figure 5.** Relationship between lateralized (LH-RH) motor connectivity and Overflow scores.



**Figure 6.** Relationship between lateralized (LH-RH) connectivity in the M1/rostral-SMC region pair and Overflow scores.

in that they observed for both right and left sided movements and they are consistent with current understanding of regional contributions to motor control. A number of studies have implicated the basal ganglia in movement speed including animal studies (DeLong, Georgopoulos, et al. 1984; van Donkelaar et al. 2000) and human studies (Turner et al. 1998; Debaere et al. 2004). Further, some have specifically implicated basal ganglia inputs to the thalamus as influencing the speed of and timing of behavioral actions (O'Boyle et al. 1996; Matell and Meck 2000). This is consistent with the currently observed association between lateralized basal ganglia-thalamic connectivity and speed of movements. Whereas basal ganglia inputs influence the speed of actions, the cerebellum plays a more central role in the relative timing of individual movements (Ivry 1997; Ivry and Spencer 2004).

The role of the cerebellum in movement timing (Ivry 1997; Ivry and Spencer 2004) is consistent with the finding that cerebellum-SMC connectivity affects dysrhythmia. In addition, studies have found that the SMC affects the rhythm of movements (Halsband et al. 1993) and response selection (Picard and Strick 2001; Simmonds et al. 2008), which suggests that SMC-cerebellar connectivity may be particularly crucial for the timing and coordination of sequential movements.

### ***Motor Network Lateralization***

Functional and structural asymmetry between the hemispheres is found throughout the human brain (Toga and Thompson 2003) and there is evidence that such lateralization may begin in utero (Previc 1991; Sun et al. 2006; Sun and Walsh 2006). Lateralization is well known within the language system (Broca 1861; Wernicke 1874) and for motor function (Amunts et al. 1996; Volkmann et al. 1998; Solodkin et al. 2001; Guye et al. 2003; Serrien et al. 2006), with left-hemisphere dominance present in most individuals.

Although there is evidence that functional lateralization is present within the motor network, its relationship to motor abilities is not clear. In right-handed subjects, task activation for unilateral movements in contralateral M1 is generally more extensive on the left than it is on the right (Volkmann et al. 1998; Scholz et al. 2000) and whole-brain connectivity with left M1 is more extensive than for right M1 (Guye et al. 2003). The current study did not examine the extent of network activity and instead examined the strength of connectivity within the a priori-defined motor network. Although mean connectivity for the left and right hemispheres was not significantly different, the degree of lateralization within the motor network was strongly related to individual differences in motor performance. Individuals with more left-lateralized connectivity across the motor network tended to have better motor performance.

The association between left-hemisphere motor dominance and motor performance may be due to a few potential factors. One possibility is that for right-handed individuals, right-side movements are more practiced than left-side movements. Because the right side is preferred, greater use could lead to stronger connectivity within the contralateral LH motor circuit. A number of previous studies have found practice-related functional changes within motor regions. Increases in task activation (Grafton et al. 1992; Carel et al. 2000) and changes in motor representations (Karni et al. 1995; Nudo 2006) are associated with motor training. Other studies found decreases

in task activation with motor sequence training (Landau and D'Esposito 2006; Sun et al. 2007), which suggests that practice-related changes in task activation are task dependent. Practice has also been associated with an increase in the strength of functional connectivity within motor regions (Wu et al. 2008). Therefore, stronger LH-lateralized connectivity could be related to more frequent use of the right side. It is interesting to note that within the current sample of right-handed children, hand preference as assessed by the Edinburgh Handedness Inventory (Oldfield 1971) was not significantly related to children's lateralized hemispheric connectivity or to their motor abilities. While stronger left-lateralized connectivity may be related to more frequent use, it seems to be unrelated to the degree of right-hand preference in right-handed TD children.

Alternatively, it is possible that the establishment of dominant left hemisphere motor connectivity is itself a process that contributes to development of motor control. A number of studies have found functional differences between the two hemispheres within motor control regions (for review, see Serrien et al. 2006). A study examining lesions in the LH or RH suggests that the LH may be more involved in the control of movement trajectory, whereas the RH may be more involved in controlling the final movement position (Haaland et al. 2004). Other studies have implicated the left hemisphere in planning of movement sequences and movement complexity (Haaland et al. 2004; Schluter et al. 1998; Verstynen et al. 2005), praxis/tool use (Bohlhalter et al. 2009; Kroliczak and Frey 2009), and bimanual coordination (Jancke et al. 2003; Serrien et al. 2003), while the RH has been implicated in spatial aspects of motor control (Garavan et al. 1999; Ghilardi et al. 2000; Schumacher et al. 2003). Many of these studies find functional lateralization within associative regions related with motor control (i.e., premotor and parietal) in addition to the basic motor regions detailed in the current study. Therefore, functional lateralization may extend beyond regions involved in basic motor control (i.e., movement execution and selection) to networks involved in more associative control (i.e., goal-directed planning and selection). The current results suggest that individuals with greater dependence on functions subserved by the left hemisphere may have better motor performance.

### ***Future Directions***

The current study is the first to establish a relationship between left-hemisphere dominance of intrinsic connectivity in the motor network and children's motor abilities. Further study is needed to establish whether this brain-behavior relationship is due to differences in experience and/or function between the two hemispheres. Examination of the relationship between handedness may also help to distinguish these possibilities. There was no relationship between hand preference and left-hemisphere lateralization or motor abilities in the current group of right-handed children. However, it is possible that such a relationship would be observed in non-right-handed individuals.

The current study identified brain-behavior relationships for motor control in 8–12 year old children and it would be useful to extend these conclusions to different developmental stages. The examination of developmental changes in these relationships could help to determine: 1) How early in development lateralization is related to motor abilities, 2) Whether this relationship persists into adulthood, and 3) Whether this



brain-behavior relationship is consistent across the lifespan. We might expect that adult motor abilities would also be related to lateralization since there were no age effects in the current sample. However, previous studies have suggested that motor abilities are still developing beyond 12 years of age (Larson et al. 2007; Cole et al. 2008) as is the motor control network (Fair et al. 2010; Jolles et al. 2010). Besides the maturation of the motor network, maturation of other systems could compensate for poor motor abilities and therefore, the relationship between lateralized connectivity and motor ability may not be as apparent in older individuals. Regardless, it would be interesting to determine whether there is a similar relationship between lateralized functional connectivity and motor control in other age groups as well as in neurological disorders which affect the motor system such as ADHD and autism.

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## Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>

## Notes

A.D.B. and P.S. are coauthors. A.D.B. wrote the paper and performed the analyses. P.S. preprocessed the data and wrote scripts for data processing. *Conflict of Interest*: Dr Pekar serves as Manager of the F.M. Kirby Research Center, which receives support from Philips Health Care, which makes the MRI scanners used in this study.

## References

- Akkal D, Dum RP, Strick PL. 2007. Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J Neurosci*. 27:10659-10673.
- Alexander GE, DeLong MR, Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 9:357-381.
- Amunts K, Schlaug G, Schleicher A, Steinmetz H, Dabringhaus A, Roland PE, Zilles K. 1996. Asymmetry in the human motor cortex and handedness. *Neuroimage*. 4:216-222.
- Barnes KA, Cohen AL, Power JD, Nelson SM, Dosenbach YB, Miezin FM, Petersen SE, Schlaggar BL. 2010. Identifying Basal Ganglia divisions in individuals using resting-state functional connectivity MRI. *Front Syst Neurosci*. 4:18.
- Behzadi Y, Restom K, Liao J, Liu TT. 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage*. 37:90-101.
- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 34:537-541.
- Bohlhalter S, Hattori N, Wheaton L, Fridman E, Shamim EA, Garraux G, Hallett M. 2009. Gesture subtype-dependent left lateralization of praxis planning: an event-related fMRI study. *Cereb Cortex*. 19:1256-1262.
- Broca P. 1861. Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bull Soc Anat Paris*. 6:330-357.
- Carel C, Loubinoux I, Boulanouar K, Manelfe C, Rascol O, Celsis P, Chollet F. 2000. Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects. *J Cereb Blood Flow Metab*. 20:478-484.
- Cole WR, Mostofsky SH, Larson JC, Denckla MB, Mahone EM. 2008. Age-related changes in motor subtle signs among girls and boys with ADHD. *Neurology*. 71:1514-1520.
- Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. 2006. Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A*. 103:13848-13853.
- Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. 2004. Cerebellar and premotor function in bimanual coordination: parametric neural responses to spatiotemporal complexity and cycling frequency. *Neuroimage*. 21:1416-1427.
- DeLong MR, Alexander GE, Georgopoulos AP, Crutcher MD, Mitchell SJ, Richardson RT. 1984. Role of basal ganglia in limb movements. *Hum Neurobiol*. 2:235-244.
- DeLong MR, Georgopoulos AP, Crutcher MD, Mitchell SJ, Richardson RT, Alexander GE. 1984. Functional organization of the basal ganglia: contributions of single-cell recording studies. *Ciba Found Symp*. 107:64-82.
- Denckla MB. 1973. Development of speed in repetitive and successive finger-movements in normal children. *Dev Med Child Neurol*. 15:635-645.
- Denckla MB. 1974. Development of motor co-ordination in normal children. *Dev Med Child Neurol*. 16:729-741.
- Denckla MB. 1985. Revised neurological examination for subtle signs (1985). *Psychopharmacol Bull*. 21:773-800.
- Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z, Biswal B, Walters JR, Castellanos FX, Milham MP. 2008. Functional connectivity of human striatum: a resting state FMRI study. *Cereb Cortex*. 18:2735-2747.
- Dubois J, Hertz-Pannier L, Cachia A, Mangin JF, Le Bihan D, Dehaene-Lambertz G. 2009. Structural asymmetries in the infant language and sensori-motor networks. *Cereb Cortex*. 19:414-423.
- Fair DA, Bathula D, Mills KL, Dias TG, Blythe MS, Zhang D, Snyder AZ, Raichle ME, Stevens AA, Nigg JT, et al. 2010. Maturing thalamo-cortical functional connectivity across development. *Front Syst Neurosci*. 4:10.
- Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A*. 102:9673-9678.
- Fuentes CT, Mostofsky SH, Bastian AJ. 2009. Children with autism show specific handwriting impairments. *Neurology*. 73:1532-1537.
- Garavan H, Ross TJ, Stein EA. 1999. Right hemispheric dominance of inhibitory control: an event-related functional MRI study. *Proc Natl Acad Sci U S A*. 96:8301-8306.
- Garvey MA, Barker CA, Bartko JJ, Denckla MB, Wassermann EM, Castellanos FX, Dell ML, Ziemann U. 2005. The ipsilateral silent period in boys with attention-deficit/hyperactivity disorder. *Clin Neurophysiol*. 116:1889-1896.
- Ghilardi M, Ghez C, Dhawan V, Moeller J, Mentis M, Nakamura T, Antonini A, Eidelberg D. 2000. Patterns of regional brain activation associated with different forms of motor learning. *Brain Res*. 871:127-145.
- Gidley Larson JC, Mostofsky SH. 2006. Motor deficits in autism. In: Tuchman R, Rapin I, editors. *Autism: a neurological disorder of early brain development*. London: Mac Keith Press for the International Review of Child Neurology Series.
- Grafton ST, Mazziotta JC, Presty S, Friston KJ, Frackowiak RS, Phelps ME. 1992. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *J Neurosci*. 12:2542-2548.
- Guye M, Parker GJ, Symms M, Boulby P, Wheeler-Kingshott CA, Salek-Haddadi A, Barker GJ, Duncan JS. 2003. Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo. *Neuroimage*. 19:1349-1360.
- Haaland KY, Elsinger CL, Mayer AR, Durgerian S, Rao SM. 2004. Motor sequence complexity and performing hand produce differential patterns of hemispheric lateralization. *J Cogn Neurosci*. 16:621-636.

- Habas C. 2010. Functional imaging of the deep cerebellar nuclei: a review. *Cerebellum*. 9:22-28.
- Haber SN, Calzavara R. 2009. The cortico-basal ganglia integrative network: the role of the thalamus. *Brain Res Bull*. 78:69-74.
- Halsband U, Ito N, Tanji J, Freund HJ. 1993. The role of premotor cortex and the supplementary motor area in the temporal control of movement in man. *Brain*. 116(Pt 1):243-266.
- Holden EW, Tarnowski KJ, Prinz RJ. 1982. Reliability of neurological soft signs in children: reevaluation of the PANESS. *J Abnorm Child Psychol*. 10:163-172.
- Holsapple JW, Preston JB, Strick PL. 1991. The origin of thalamic inputs to the "hand" representation in the primary motor cortex. *J Neurosci*. 11:2644-2654.
- Iverson JM. 2010. Developing language in a developing body: the relationship between motor development and language development. *J Child Lang*. 37:229-261.
- Ivry R. 1997. Cerebellar timing systems. *Int Rev Neurobiol*. 41:555-573.
- Ivry RB, Spencer RM. 2004. The neural representation of time. *Curr Opin Neurobiol*. 14:225-232.
- Jancke L, Specht K, Shah JN, Hugdahl K. 2003. Focused attention in a simple dichotic listening task: an fMRI experiment. *Brain Res Cogn Brain Res*. 16:257-266.
- Jolles DD, van Buchem MA, Crone EA, Rombouts SA. 2010. A comprehensive study of whole-brain functional connectivity in children and young adults. *Cereb Cortex*. 21:385-391.
- Karni A, Meyer G, Jezzard P, Adams MM, Turner R, Ungerleider LG. 1995. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature*. 377:155-158.
- Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP. 1993. Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. *Science*. 261:615-617.
- Konczak J, Timmann D. 2007. The effect of damage to the cerebellum on sensorimotor and cognitive function in children and adolescents. *Neurosci Biobehav Rev*. 31:1101-1113.
- Kooistra CA, Heilman KM. 1988. Motor dominance and lateral asymmetry of the globus pallidus. *Neurology*. 38:388-390.
- Krienen FM, Buckner RL. 2009. Segregated fronto-cerebellar circuits revealed by intrinsic functional connectivity. *Cereb Cortex*. 19:2485-2497.
- Kroliczak G, Frey SH. 2009. A common network in the left cerebral hemisphere represents planning of tool use pantomimes and familiar intransitive gestures at the hand-independent level. *Cereb Cortex*. 19:2396-2410.
- Landau SM, D'Esposito M. 2006. Sequence learning in pianists and nonpianists: an fMRI study of motor expertise. *Cogn Affect Behav Neurosci*. 6:246-259.
- Larson JC, Mostofsky SH, Goldberg MC, Cutting LE, Denckla MB, Mahone EM. 2007. Effects of gender and age on motor exam in typically developing children. *Dev Neuropsychol*. 32:543-562.
- Lin W, Zhu Q, Gao W, Chen Y, Toh CH, Styner M, Gerig G, Smith JK, Biswal B, Gilmore JH. 2008. Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain. *AJNR Am J Neuroradiol*. 29:1883-1889.
- Lisberger SG. 2010. Visual guidance of smooth-pursuit eye movements: sensation, action, and what happens in between. *Neuron*. 66:477-491.
- Matell MS, Meck WH. 2000. Neuropsychological mechanisms of interval timing behavior. *Bioessays*. 22:94-103.
- Menon V, Adelman NE, White CD, Glover GH, Reiss AL. 2001. Error-related brain activation during a Go/NoGo response inhibition task. *Hum Brain Mapp*. 12:131-143.
- Middleton FA, Strick PL. 1997. Cerebellar output channels. *Int Rev Neurobiol*. 41:61-82.
- Mostofsky SH, Burgess MP, Gidley Larson JC. 2007. Increased motor cortex white matter volume predicts motor impairment in autism. *Brain*. 130:2117-2122.
- Mostofsky SH, Powell SK, Simmonds DJ, Goldberg MC, Caffo B, Pekar JJ. 2009. Decreased connectivity and cerebellar activity in autism during motor task performance. *Brain*. 132:2413-2425.
- Mostofsky SH, Rimrodt SL, Schafer JG, Boyce A, Goldberg MC, Pekar JJ, Denckla MB. 2006. Atypical motor and sensory cortex activation in attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study of simple sequential finger tapping. *Biol Psychiatry*. 59:48-56.
- Mostofsky SH, Simmonds DJ. 2008. Response inhibition and response selection: two sides of the same coin. *J Cogn Neurosci*. 20:751-761.
- Nachev P, Kennard C, Husain M. 2008. Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci*. 9:856-869.
- Nudo RJ. 2006. Plasticity. *NeuroRx*. 3:420-427.
- O'Boyle DJ, Freeman JS, Cody FW. 1996. The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease. *Brain*. 119(Pt 1):51-70.
- Oldfield RC. 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 9:97-113.
- Picard N, Strick PL. 2001. Imaging the premotor areas. *Curr Opin Neurobiol*. 11:663-672.
- Postuma RB, Dagher A. 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb Cortex*. 16:1508-1521.
- Previc FH. 1991. A general theory concerning the prenatal origins of cerebral lateralization in humans. *Psychol Rev*. 98:299-334.
- Robinson S, Basso G, Soldati N, Sailer U, Jovicich J, Bruzzone L, Kryspin-Exner I, Bauer H, Moser E. 2009. A resting state network in the motor control circuit of the basal ganglia. *BMC Neurosci*. 10:137.
- Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, et al. 2001. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage*. 13:250-261.
- Sala R, Granero R, Ezpeleta L. 2006. Dimensional analysis of a categorical diagnostic interview: the DICA-IV. *Psicothema*. 18:123-129.
- Schluter ND, Rushworth MF, Passingham RE, Mills KR. 1998. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. A study using transcranial magnetic stimulation. *Brain*. 121 (Pt 5):785-799.
- Scholz VH, Flaherty AW, Kraft E, Keltner JR, Kwong KK, Chen YI, Rosen BR, Jenkins BG. 2000. Laterality, somatotopy and reproducibility of the basal ganglia and motor cortex during motor tasks. *Brain Res*. 879:204-215.
- Schumacher EH, Elston PA, D'Esposito M. 2003. Neural evidence for representation-specific response selection. *J Cogn Neurosci*. 15:1111-1121.
- Serrien DJ, Cassidy MJ, Brown P. 2003. The importance of the dominant hemisphere in the organization of bimanual movements. *Hum Brain Mapp*. 18:296-305.
- Serrien DJ, Ivry RB, Swinnen SP. 2006. Dynamics of hemispheric specialization and integration in the context of motor control. *Nat Rev Neurosci*. 7:160-166.
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, Clasen L, Evans A, Giedd J, Rapoport JL. 2007. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A*. 104:19649-19654.
- Simmonds DJ, Pekar JJ, Mostofsky SH. 2008. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*. 46:224-232.
- Solodkin A, Hlustik P, Noll DC, Small SL. 2001. Lateralization of motor circuits and handedness during finger movements. *Eur J Neurol*. 8:425-434.
- Sun FT, Miller LM, Rao AA, D'Esposito M. 2007. Functional connectivity of cortical networks involved in bimanual motor sequence learning. *Cereb Cortex*. 17:1227-1234.
- Sun T, Collura RV, Ruvolo M, Walsh CA. 2006. Genomic and evolutionary analyses of asymmetrically expressed genes in human fetal left and right cerebral cortex. *Cereb Cortex*. 16(Suppl 1):i18-i25.
- Sun T, Walsh CA. 2006. Molecular approaches to brain asymmetry and handedness. *Nat Rev Neurosci*. 7:655-662.
- Suskauer SJ, Simmonds DJ, Caffo BS, Denckla MB, Pekar JJ, Mostofsky SH. 2008. fMRI of intrasubject variability in ADHD:



- anomalous premotor activity with prefrontal compensation. *J Am Acad Child Adolesc Psychiatry.* 47:1141-1150.
- Toga AW, Thompson PM. 2003. Mapping brain asymmetry. *Nat Rev Neurosci.* 4:37-48.
- Turner RS, Grafton ST, Votaw JR, DeLong MR, Hoffman JM. 1998. Motor subcircuits mediating the control of movement velocity: a PET study. *J Neurophysiol.* 80:2162-2176.
- van Donkelaar P, Stein JF, Passingham RE, Miall RC. 2000. Temporary inactivation in the primate motor thalamus during visually triggered and internally generated limb movements. *J Neurophysiol.* 83:2780-2790.
- Verstynen T, Diedrichsen J, Albert N, Aparicio P, Ivry RB. 2005. Ipsilateral motor cortex activity during unimanual hand movements relates to task complexity. *J Neurophysiol.* 93:1209-1222.
- Viholainen H, Ahonen T, Lyytinen P, Cantell M, Tolvanen A, Lyytinen H. 2006. Early motor development and later language and reading skills in children at risk of familial dyslexia. *Dev Med Child Neurol.* 48:367-373.
- Vitiello B, Ricciuti AJ, Stoff DM, Behar D, Denckla MB. 1989. Reliability of subtle (soft) neurological signs in children. *J Am Acad Child Adolesc Psychiatry.* 28:749-753.
- Volkman J, Schnitzler A, Witte OW, Freund H. 1998. Handedness and asymmetry of hand representation in human motor cortex. *J Neurophysiol.* 79:2149-2154.
- Wernicke C. 1874. *Der aphasische Symptomencomplex.* Breslau, Germany: Cohn & Weigert.
- Wu T, Chan P, Hallett M. 2008. Modifications of the interactions in the motor networks when a movement becomes automatic. *J Physiol.* 586:4295-4304.